REMARKS

Amendments to the Claims

Claims 1-3, 7-9, and 11-24 are pending in the present application. Claim 4-6 have been previously canceled. Claims 11-24 have been previously withdrawn from consideration. No amendments to the claims have been currently made.

Rejections Under 35 U.S.C. § 103(a) Over Ohtaka et al.

Claims 1-3 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hiroshi Ohtaka et al., "Benzylpiperazine derivatives. IV. Syntheses and cerebral vasodilating activities of 1-benzyl-4-diphenylmethylpiperazine derivatives", *Chemical & Pharmaceutical Bulletin*, (1987), 35 (8), 3270-5 (hereinafter referred to as "Ohtaka"). The Examiner asserts that Ohtaka teaches benzylpiperazine derivatives and their synthesis, wherein the structure of the compounds are shown in formula I of Ohtaka. The Examiner further asserts that, in formula I of Ohtaka, the substituent R2 can be 2,4-(methoxy)2C6H3. Additionally, the Examiner asserts that Ohtaka teaches a substituted piperazine ring, which, as asserted by the Examiner, meets the limitation of Applicants' claims that R1 and R2 of Applicants' formula (1) may together with the nitrogen atom to which they are attached form a C3 to C6 saturated or unsaturated ring which contains one or more additional heteroatoms selected from O, S, and N atoms.

The Examiner, however, acknowledges that the compounds of Ohtaka differ from Applicants' currently claimed compounds because Ohtaka teaches methoxy groups on the benzene ring whereas Applicants' claimed compounds require hydroxy groups. Notwithstanding, the Examiner concludes that methoxy groups are the next obvious homologs of Applicants' claimed hydroxy groups, and, thus, it would have been obvious to one of ordinary skill in the art to use either hydroxy or methoxy groups on the benzene ring of the compounds of Ohtaka with an expectation to achieve a compound having cerebral vasodilating activity. Applicants respectfully traverse the present rejection based on the following comments.

Ohtaka does not teach or suggest all of Applicants' claim limitations and, therefore, does not establish a *prima facie* case of obviousness. *See* MPEP 2143.03. As currently presented, Applicants' claim 1 is directed to a compound of claimed formula (1) wherein R_1 and R_2 are selected from respective lists of substituents as defined in the

claim, or R_1 and R_2 together with the nitrogen atom to which they are attached form a C_3 to C_6 saturated or unsaturated ring containing in the ring one or more additional hetero atoms selected from O, S, and N. Applicants' claimed formula (1) requires that the benzene ring is substituted with *hydroxy groups* at the *2-position* and the *6-position* relative to the methylene linking group at the 1-position on the benzene ring (*i.e.*, Applicants' compounds of claimed formula (1) are 2-substituted-benzene-*1,3*-diol compounds). Applicants' claimed compounds can be used as couplers for oxidative hair coloring to provide bright yellow and orange-yellow coloration to hair.

In contrast, Ohtaka fails to teach or suggest benzene compounds having hydroxy groups or methoxy groups at only the 2-position and the 6-position relative to a third substituent at the 1-position on the benzene ring. Although Ohtaka discloses that R2 of formula I of Ohtaka can be 2,4-(methoxy)2C6H3, as noted by the Examiner, the resulting compound has methoxy groups at the 2-position and the 4-position relative to the methylene group, which links the benzene ring to the substituted piperazine ring, at the 1-position of the benzene ring. Aside from a 2,4-(methoxy)benzene group, Ohtaka further discloses that R2 of formula (I) of Ohtaka may be a 2,3,4-(methoxy)benzene group, a 3,4,5-(methoxy)benzene group, a 2,4,6-(methoxy)benzene group, and a 2,3-(methoxy)benzene group. None of these R2 substituents results in methoxy-substituted benzene compounds which are analogous to Applicants' claimed compounds which have hydroxy groups at *only* the 2-position and the 6-position relative to the methylene linking group at the 1-position on the benzene ring. As a result, Mills fails to teach or suggest all of the limitations of Applicants' claim 1.

Additionally, there is no motivation to modify the compounds disclosed in Ohtaka to achieve Applicants' compounds of claim 1. Even though, as discussed above, Ohtaka discloses that a 2,4,6-(methoxy)benzene group is among the possible R2 substituents in formula I of Ohtaka, one of ordinary skill in the art would not be motivated to use a 2,6-(methoxy)benzene group instead of the 2,4,6-(methoxy)benzene group. The replacement of a methoxy group at the 4-position with a hydrogen could affect the compound's pharmacological activity and other physical properties as well as the ability to synthesize the compound.

Further, the other possible R2 substituents disclosed in Ohtaka teach against the selection of a 2,6-(methoxy)benzene group. More particularly, all of the other disclosed

possible R2 substituents, which are benzene rings substituted with two or more methoxy groups, are substituted with methoxy at adjacent positions on the benzene ring (*e.g.*, "2,3,4-" and "3,4,5-") or at no more than every other position on the benzene ring (*e.g.*, "2,4-" and "2,4,6-"). Notably, Ohtaka does not disclose any R2 substituents in which methoxy groups are substituted on a benzene ring such that more than one unsubstituted position is present between each of the methoxy-substituted positions. Thus, the disclosure of Ohtaka teaches against a benzene group substituted with methoxy only at the 2-position and the 6-position relative to a third substituent at the 1-position.

Accordingly, a *prima facie* case of obviousness has not been established because Ohtaka fails to teach or suggest all of the limitations of Applicants' claim 1 and further fails to provide any motivation to modify the compounds of Ohtaka to achieve Applicants' claimed compounds. Therefore, Applicants' claim 1, as well as claims 2-3 which contain the limitations of claim 1, are novel and unobvious over Ohtaka.

Rejections Under 35 U.S.C. § 103(a) Over Ohtaka et al. in view of U.S. Patent No. 4,888,283 to Bertini et al.

Claims 7-9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hiroshi Ohtaka et al., "Benzylpiperazine derivatives. IV. Syntheses and cerebral vasodilating activities of 1-benzyl-4-diphenylmethylpiperazine derivatives", *Chemical & Pharmaceutical Bulletin*, (1987), 35 (8), 3270-5 (hereinafter referred to as "Ohtaka") in view of U.S. Patent No. 4,888,283 to Bertini et al. ("Bertini"). The Examiner asserts that Ohtaka discloses benzylpiperazine derivatives, as discussed above. The Examiner then asserts that Bertini teaches compounds that act as inhibitors of benzylaminoxidases, which compounds have a general formula I in which R1 and R2 can be hydrogen, hydroxy, and alkoxy, and R3, R4, and R5 can be hydrogen or alkyl. Thus, the Examiner asserts that Bertini teaches benzene diol compounds.

The Examiner further asserts that Bertini suggests that, for compounds of formula I containing alkoxy groups at R1 and R2, the synthesis steps comprise preparing benzaldehyde from benzene, transforming the benzaldehyde to oximes, and reducing the oximes to benzylamino compounds. The Examiner acknowledges that Bertini teaches a method of preparing benzene compounds having alkoxy groups on the ring instead of hydroxy groups, as claimed by Applicants. However, the Examiner still concludes that it

would have been obvious to one of ordinary skill in the art at the time of the present invention to prepare a hydroxy containing benzene derivative or the methoxy containing benzene derivative of formula I of Ohtaka by employing the synthesis steps disclosed in Bertini because Bertini suggests that preparing compounds by such a process is advantageous and easily carried out. Applicants respectfully traverse the present rejection based on the following comments.

The combination of Ohtaka and Bertini does not teach or suggest all of Applicants' claim limitations and, therefore, does not establish a *prima facie* case of obviousness. *See* MPEP 2143.03. As currently presented, Applicants' claim 7 is directed to a process for the preparation of a compound of formula (1) of claim 1, which process comprises the steps of (a) reacting an 2,5-dimethoxy-benzaldehyde of formula (2) as claimed with a reagent of the formula R_1R_2NH and a reductive amination reducing agent to produce a compound of formula (3) as claimed, and (b) deprotecting the compound of formula (3) by reacting with a deprotection agent *producing a compound of formula (1) as claimed in claim 1*. Thus, Applicants' claim 7 contains the limitations of claim 1.

As discussed above, Applicants' claim 1 is directed to a compound of claimed formula (1), wherein R_1 is selected from hydrogen atoms, C_1 to C_5 alkyl, C_1 to C_5 mono or dihydroxyalkyl, and phenyl or benzyl optionally substituted with a hydroxyl, amino or C_1 to C_3 alkoxy group, and R_2 is selected from *C_1 to C_5 mono or dihydroxyalkyl, and phenyl or benzyl optionally substituted with a hydroxyl, amino or C_1 to C_3 alkoxy group*, or R_1 and R_2 together with the nitrogen atom to which they are attached form certain heterocyclic rings as claimed. Additionally, as depicted in claimed formula (1), Applicants' claimed compounds require that the benzene ring is substituted with *hydroxy groups* at the *2-position* and the *6-position* relative to the methylene linking group at the 1-position on the benzene ring (*i.e.*, Applicants' compounds of claimed formula (1) are 2-substituted-benzene-*1,3*-diol compounds). Applicants' claimed compounds can be used as couplers for oxidative hair coloring to provide bright yellow and orange-yellow coloration to hair.

In contrast, neither Ohtaka nor Bertini, alone or in combination, teaches or suggests a process for the preparation of compounds as claimed by Applicants in claim 1. As discussed above, Ohtaka fails to teach or suggest benzene compounds having hydroxy groups or methoxy groups at *only* the 2-position and the 6-position relative to a third

substituent at the 1-position on the benzene ring. Separately, Bertini fails to teach or suggest benzene compounds having a substituted aminomethyl group at the 1- position of the benzene ring relative to hydroxy substituents at the 2- and 6-positions. Although the variable substituents of formula I of Bertini can be selected such that any two of the R1-R5 substituents are hydroxy, which thus provide a benzene diol compound, formula I of Bertini requires an *unsubstituted* aminomethyl group at the position on the benzene ring between the R1 and R2 substituents. Bertini provides no teaching or suggestion for a *hydroxyalkyl-substituted* or a *phenyl- or benzyl-substituted* aminomethyl group at this position of the benzene ring.

In formula (1) of Applicants' claim 1 as currently presented, R_2 cannot be hydrogen or C_1 to C_5 alkyl, and, therefore, an aminomethyl group *substituted with hydroxyalkyl or phenyl or benzyl* is required at the 2-position of the benzene-1,3-diol derivative compound. Alternatively, Applicants' R_1 and R_2 may together with the nitrogen atom to which they are attached form a ring structure, as claimed. However, as stated above, Bertini requires an *unsubstituted* aminomethyl group at the position on the benzene ring, and, thus, does not allow for a ring structure which incorporates the nitrogen atom of the aminomethyl group. Consequently, Bertini fails to teach or suggest all of the limitations of Applicants' claim 1.

Additionally, there is no motivation to combine the teachings of Ohtaka and Bertini to attempt to achieve a process as claimed by Applicants in claim 7 for the preparation of compounds as claimed by Applicants in claim 1. Ohtaka is directed to benzylpiperazine derivatives which demonstrate cerebral vasodilating activity, and, in contrast, Bertini is directed to aminomethylbenzene compounds which may have additional substituents at one or more positions on the benzene ring and which are useful as inhibitors of benzylaminoxidases. The compounds of Ohtaka are based on a piperazine ring which is substituted with benzyl and phenyl substituents. The compounds of Bertini are based on a benzene ring which is substituted with an aminomethyl substituent and optionally other substituents. However, the compounds of Bertini do not include the possibility of a piperazine ring or any other saturated hydrocarbon ring structure containing one or more heteroatom. Thus, one of ordinary skill in the art would not look to the process disclosed in Bertini in an effort to make the compounds of Ohtaka.

Moreover, because Ohtaka itself discloses synthesis methods for the compounds of Ohtaka, one of ordinary skill in the art would not be motivated to look beyond the teachings of Ohtaka, much less specifically to the teaching of Bertini, in order to make the compounds of Ohtaka. Consequently, there is no motivation to combine the teachings of Ohtaka and Bertini to attempt to achieve a process as claimed by Applicants in claim 7 for the preparation of compounds as claimed by Applicants in claim 1.

Accordingly, a *prima facie* case of obviousness has not been established because the combination of Ohtaka and Bertini fails to teach or suggest all of the limitations of Applicants' claim 7, as well as claim 1. Further, there is no motivation to combine the teachings of Ohtaka and Bertini to attempt to achieve Applicants' claimed process for preparing Applicants' claimed compounds. Therefore, Applicants' claim 7, which contains the limitations of claim 1, as well as claims 8-9 which depend from claim 7, are novel and unobvious over the combination of Ohtaka and Bertini.

CONCLUSION

In light of the remarks presented herein, it is requested that the Examiner reconsider and withdraw the present rejections. Early and favorable action in the case is respectfully requested.

Applicants have made an earnest effort to place their application in proper form and to distinguish the invention as now claimed from the applied references. In view of the foregoing, Applicants respectfully request reconsideration of this application and allowance of Claims 1-3 and 7-9.

Respectfully submitted,

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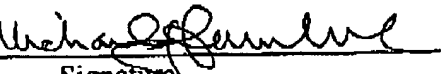
By 
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